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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	15

DATE MAILED: 08/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/528,682	Pizza et al.
Examiner	**Art Unit**
Michael Borin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 21, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *7-32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *7-32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the claims

1. Claim 7 is amended. Claims 30-32 are added. Claims 7-32 are pending.

Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Drawings

2. Submission of the Formal Drawings is noticed. The set of formal drawings is not complete as it does not contain new Fig. 12. Formal Drawings will not be reviewed by a draftsman until complete.

A the same time, the proposed drawing Fig. 12, filed on 6/6/02 has been disapproved because it introduces new matter into the drawings. 37 CFR 1.121(a)(6) states that no amendment may introduce new matter into the disclosure of an application. The original disclosure does not support the showing of sequences as now presented on Fig. 12.

Claim Rejections - 35 U.S.C. § 112, first paragraph.

3. Claims 7-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are amended to read on SEQ ID No. 1. This sequence has not been described in the specification as originally filed. Applicant asserts that the sequence has been described in Domenighini et al, 1995 reference, which is incorporated by reference. It appears that said reference is not present in this file (please provide a copy); therefore, Examiner based his determination on preceding WO 93/13202 patent of Domenighini et al. Which describes porcine LT-A on Fig. 2a. The sequence of porcine LT-A in the reference differs from instantly presented SEQ ID No. 1 of porcine LT-A at least in that it differs in other parts of the sequence (e.g., residues 19,20) and that Ala residue is in position 71, rather than 72. Further, as was stated previously, there is no incorporation by reference of any particular sequence. In the instant case, incorporation a sequence by reference is improper as it is an essential material which has to be explicitly presented in the instant case. See MPEP 608(p):

> "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3)describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference.

Applicant argues that "particular sequences of various LT-A proteins are incorporated by reference" and addresses to p. 10, lines 28-30 of the specification. Said part of the specification merely states that every reference addressed in the specification is incorporated by reference; no more specific comments are offered. Such incorporation by reference is improper because a mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication and direct to specific portions of the referenced document where the subject matter being incorporated may be found. See MPEP 608.01(p).

4. Similarly, claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims recite SEQ ID Nos 2-4. These sequence have not been described in the specification as originally filed.

5. Claims 7-29 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The claims are drawn to polynucleotides encoding a sequence of subunit A of E.Coli toxin, LT-A, wherein Ala residue at position 72 is replaced with Arg residue; further, the claims are drawn to corresponding vectors and host cells. As there is a plurality of LT-A proteins and only proteins having a replaced Ala residue in position 72 are subject of invention, the presence of Ala/Arg in position 72 is critical and essential to the practice of the invention. However, no particular LT-A having sequence with Ala or Arg in the indicated position 72 is included in the claims or enabled by the disclosure. Multiple descriptions in the prior art cited in the specification refer to plurality of products, not necessarily comprising Ala^{72}. For example, specification, p. 5, line 25 +, describes LT-A proteins having not Ala^{72}, but a residue "which corresponds to Ala^{72}". However, no particular LT-A having sequence with Ala in the indicated position is included in the claims or is present in the specification. Accordingly, the claims and the specification lack the essential subject matter. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

6. Claims 7-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn, in part, to polynucleotides encoding immunogenic fragments of LT-A comprising at least eight residues. There is no description in the claims or specification describing said fragments in such detail that will sufficiently identify the epitope sequence. Specification recites fragments containing Ala-72 residue (p. 5, lines 14-15). However, the cited description merely states that a fragment should contain Ala residue (which is further replaced). Location of this residue is irrelevant because only a single residue is identified and thus any Ala residue will satisfy this structural requirement as no other structural characteristics (e.g., the nature of other residues present in the fragment and their relation to the sequence of LT-A) are identified. There is no guidance on core structure of said fragment which would render a "immunological fragment" as claimed. The mere presence of arginine (i.e., the residue substituting Ala) is not sufficient for identification of a core structure. As there are no sufficient structural characteristics are present for the LT-A fragment, there are no sufficient structural characteristics for DNA encoding thereof, and correspondent vectors, host cells and uses thereof.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 7-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

Claim 7 as amended is ambiguous in relation to the structure of the product claimed. The claim provides conflicting structural characteristics of the product : from one side it requires presence of an Ala residue in the LT-A fragment; from another side, it requires absence of this said Ala residue.

Claims 30-32: In addition to ambiguity of claim 7, its dependent claims are confusing as the product of claim 7 is a derivative of porcine LT-A, and, according to claims 30-32, it is supposed to comprise residues of human LT-A. It is noted in Fig. 12 comparing human and porcine sequences that they do not have a high degree of similarity.

Claim Rejections - 35 USC § 102 and 103.

8. Claims 7-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 145486. The rejection is maintained for the following re-iterated reasons of record:

The patent teaches compositions and vaccines comprising modified LT-A of the following original sequences, respectively:

1 MKNITFIFFI LLASPLYANG DRLYRADSRP PDEIKRSGGL MPRGHNEYFD
51 RGTQMNINLY DHARGTE**TGF VRYDDG**YVST SLSLRSAHLA GQFILSGYST
101 YYIYVIATAP NMFNVNDVLG VYSPHPYEQE VSALGGIPYS QIYGWYRVNF
151 GVIDERLHRN REYRDRYYRN LNIAPAEDGY RLAGFPPDHQ AWREEPWIHH
201 APQGCGNSSR TITGDTCNEE TQNLSTIYLR EYQSKVKRQI FSDYQSQVDI

The referenced protein comprises sequence TGFVRYDDG (underlined), which is a fragment of subunit LT-A having Arg residue instead of Ala. As the referenced protein presents a practical interest, as it can be used as an immunogenic stimulant and vaccine, one would be motivated to produce such protein recombinantly using conventional methods of molecular biology. Further, in regard to the second immunogenic component, because combination therapies for generation of immune response are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the effectiveness of the treatment, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the immunogenic subunit LT-A in combination with

another immunogenic antigen. Modification to combine components all known to be useful as immunogenic agents would have been obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be useful for the very same purpose. Consequently, it would have been obvious to produce such conjugate protein recombinantly using conventional methods of molecular biology.

Response to arguments

Applicant argues that the position of Arg residue does not correspond to position 72 of Ala in SEQ ID No. 1. Aside from the fact that SEQ ID No. 1 is a new matter (see above), the only meaning that Examiner reads into the limitation that the fragment comprises "amino acids residue corresponding to Ala-72 of SEQ ID No. 1" is that the residue which is being replaced as claimed has to be a residue corresponding to Ala,, i.e., it has to be any Ala replaced by any, in this case, Arg residue. Any Ala residue will be "corresponding" to any other Ala residue because they are the same by their nature.

9. Claims 7-29 are rejected under 35 U.S.C. 102(b) as anticipated by Burnette et al (US Patent 5,770,203).

The reference teaches nucleic acid (SEQ ID No. 1) encoding cholera toxin, modified cholera toxins, nucleic acids, vectors and host cells corresponding thereto. The toxin comprises fragment 29-54 of the instantly claimed SEQ ID No. 1 (see sequence allignment attached), said fragment containing a plurality of Arg residues (see, e.g., residues 33, 54). Therefore, the reference teaches nucleic acid encoding fragment of LT-A containing Arg residue. Although the reference does not teach that the Arg residue originated from a replacement of an Ala residue, the referenced product satisfies the structural limitation of instant claim to contain an Arg residue. As to the description of the location of (nonexistent) Ala residue, the only meaning that Examiner reads into the limitation that the claimed product contains Arg residue which is located in place where any Ala residue might have been located as well.

Abstract

10. The abstract of the disclosure is objected to because it contains new matter. See rejections under 112, first paragraph above. Correction is required. See MPEP § 608.01(b).

Conclusion.

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 5, 2002

mlb

MICHAEL BORIN, PH.D
PRIMARY EXAMINER